Clinical Efficacy and Safety Review

BLA #:	97-1251
Product:	Simulect® [basiliximab, chimeric (murine/ human) monoclonal antibody [redacted] purified glycosylated protein, MW=144 kDa, [redacted] against the IL-2 receptor alpha chain (IL-2Rα, Tac, CD25)] concentrate (20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate, 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP).
Clinical indication:	*"...prophylaxis of organ rejection in de novo renal transplantation. Simulect™ should be used with Neoral® (cyclosporine for microemulsion) and corticosteroid-based immunosuppression."*
Sponsor:	Novartis Pharmaceuticals
Receipt date:	11-12-97
Assignment date:	11-26-97
Amendment dates:	12-08-97; 03-19-98.
Final action date:	05-11-98
Sections reviewed:	Clinical efficacy and safety
# volumes:	29-92 of 93
Reviewer:	David M. Essayan, M.D.
Review completion date:	04-30-98

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDR, complementarity-determining region; CyA, cyclosporine A; ELISA, enzyme-linked immunosorbant assay; Fab, the antigen binding domain of the immunoglobulin molecule; Fc, the constant region of the immunoglobulin molecule; GVHD, graft vs. host disease; HAMA, human anti-mouse antibody; HACA, human anti-chimera antibody; Ig, immunoglobulin; IL-, interleukin; ITT, intent-to-treat; kD, kilodaltons; PBMC, peripheral blood mononuclear cells; $t_{1/2}$, half life; Tac, T cell activation antigen, p55, the α chain of the IL-2 receptor (IL-2Rα); Tx, transplant.

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Abstract:

Simulect® (basiliximab, Novartis Pharmaceuticals) is a chimeric monoclonal antibody derived from a murine anti-human interleukin 2 receptor α chain monoclonal antibody; the final product exhibits strict species specificity for primate IL-2Rα. The binding of this Ab to its target interrupts IL-2/IL-2R interaction, resulting in inhibition of IL-2 induced T cell activation via the high-affinity IL-2 receptor; concurrent activation of ADCC by the Fc portion of the product may induce clearance of the reactive T cell clones and augment selective immunosuppression. This document reviews and summarizes the clinical efficacy and safety data of the BLA application of Simulect® (97-1251) for use in the prevention of acute rejection episodes in first renal transplant patients receiving concomitant immunosuppression with steroids and Neoral® (cyclosporine for microemulsion).

1. Introduction:

Organ rejection remains the single largest post-operative impediment to success in renal transplantation. 80-90% of first ejection episodes occur within the first 6 weeks following transplantation. Acute renal allograft rejection is the most common cause of short-term graft loss and is inversely correlated with long-term graft function and graft survival (93 vs. 85% at 1 year; 89 vs. 67% at 5 years). Episodes of acute renal allograft rejection lead to graft failure in an even greater proportion of secondary recipients; moreover, such rejection episodes and the measures taken to reverse them contribute significantly to the morbidity, mortality, and cost associated with renal transplantation.

In the forty years since the first renal transplant was performed, pre-, peri-, and post-surgical immunomodulation has been progressively refined in order to prevent rejection while minimizing complications associated with immunosuppression and general toxicity. One such approach targets activation-induced signals between immune cells; many currently used chemical immunomodulators (cyclosporin, tacrolimus) interrupt T cell activation by blocking IL-2 generation, thus abrogating ongoing immune responses. An alternative mechanism, utilized by the current product, blocks IL-2 signaling by inhibition of IL-2 receptor engagement.

Simulect is a chimeric monoclonal antibody (predicted molecular weight of 144 kD) derived from a murine anti-human — Tac) monoclonal antibody by

5 lines

Simulect is proposed for use as an adjunct to standard induction immunosuppressive therapy in renal transplant recipients.

The remainder of this review will follow the outline of the original, submitted annotated package insert (section 2A); exact quotes from this document (*in bold italics*) will be analyzed, with additional relevant information provided in appropriate areas.

Overview of Clinical Trials

Study No.	Design	Simulect™ Dose (Total mg)	No. of Patients Enrolled Simulect™	Placebo

Total no. of patients: (excluding

Summary of Uncontrolled Clinical Trials

Parameter	CHIB 101	CHIB 105	CHIB 106
Indication			
n			
Number and Location of Centers			
Study Design			
Randomization			
Type of Patient			
Study Duration			
Simulect™ Dosing Regimen**			
Background Immunosuppression			
Clinical Variables			
Pharmacokinetics/ Pharmacodynamics			

* — patients were enrolled and included in the analysis. However, one patient was randomized and received the first dose of Simulect™, but never received a renal transplant.

** Day 0 dose is given approximately ———— prior to transplant surgery.

Summary of Controlled Clinical Trials

Parameter	CHIB 352	CHIB 201
Indication	adult de novo renal transplantation	adult de novo renal transplantation
n	348 (174 Simulect™)	381 (193 Simulect™)
Number and Location of Centers	21 United States	21 Germany (8), France (4), United Kingdom (3), Canada (2), Switzerland (2), Norway (1), Belgium (1)
Study Design	randomized, double-blind, placebo-controlled, parallel-group	randomized, double-blind, placebo-controlled, parallel-group
Randomization	1:1 Simulect™: placebo	1:1 Simulect™: placebo
Type of Patient	primary, mismatched, cadaveric or living donor renal allograft recipients	primary, mismatched, cadaveric renal allograft recipients
Study Duration	1 year with 4 year follow-up	1 year with 4 year follow-up
Simulect™ Dosing Regimen**	20 mg on Day 0 and on Day 4 by intravenous infusion	20 mg on Day 0 and on Day 4 by intravenous infusion
Background Immunosuppression	cyclosporine (Neoral®) and steroids	cyclosporine (Neoral®) and steroids
Primary Efficacy Criteria	incidence of death, graft loss or acute rejection (at 6 months)	incidence of death, graft loss or acute rejection (at 6 months)
Safety Variables	occurrence and severity of adverse events (including infections), laboratory parameters, vital signs, physical exams	occurrence and severity of adverse events (including infections), laboratory parameters, vital signs, physical exams
Pharmacokinetics/ Pharmacodynamics***	1. Simulect™ serum concentrations 2. Anti-Simulect™ idiotype response 3. HAMA* response	1. Simulect™ serum concentrations (at 5 study centers)

* HAMA=human anti-mouse antibody

** Day 0 dose is given approximately two hours prior to transplant surgery.

*** Samples were collected for both treatment groups to maintain the blind at the sites. Analysis was performed by a separate laboratory for samples from the Simulect™ group only.

Efficacy Review:

The safety and efficacy of SIMULECT™ in combination with Neoral® (cyclosporine for microemulsion) and steroids for the prevention of organ rejection following allogeneic renal transplantations were assessed in two randomized, double-blind, multicenter trials. These studies compared placebo with SIMULECT™ 40 mg, administered as two 20 mg IV doses, the first dose given within 2 hours prior to transplantation surgery (Day 0) and the second dose given on Day 4 post-transplantation. The dose of SIMULECT™ was chosen to provide 30-45 days of IL-2Rα suppression. Chronic dual immunosuppressive therapy consisted of Neoral® (cyclosporine for microemulsion) and steroids, administered starting on Day 0. Patients 18-75 years of age undergoing first cadaveric or living-donor renal transplantation, with ≥1 HLA mismatch were enrolled. A total of 729 patients were enrolled in the 2 studies, of which 363 SIMULECT™-treated patients and 359 placebo-treated patients received transplants. Study 201 was conducted at 21 sites in Europe and Canada; Study 352 was conducted at 21 sites in the USA.

Segment Summary:

The working hypothesis of this sponsor through phase 1 development was that saturation of the CD25 antigen with basiliximab for 30-45 days would provide optimal clinical benefit. Saturation of CD25 was correlated with serum basiliximab levels of ≥0.2 μg/ml. The pharmacodynamic conclusion from the phase 1 studies was that "two 20 mg IV doses, the first dose given within 2 hours prior to transplantation surgery (Day 0) and the second dose given on Day 4 post-transplantation" best achieved this goal in the majority of subjects (please see review of Section 6 for complete analysis). It was this regimen that was taken forward into both phase 3 trials.

The two phase 3 studies were nearly identical in design; they were conducted contemporaneously on two continents. Both studies were randomized, double blind, placebo controlled, multi-center, multi-dose trials utilizing background double immunosuppression with cyclosporin and steroids; the prospectively designed target levels and regimens were nearly identical and the actual exposure to these agents during the trials were well matched between the placebo and basiliximab arms in both studies. Rescue medications and regimens for rejection episodes were also nearly identical.

The ITT study populations had reasonably well matched rates of discontinuation at 6 and 12 months; the rates were well within the expected range for the study design. Complete review of the CRFs of those subjects discontinued from the study revealed no specific concerns.

Demographic and disease data for the study populations were well matched between the placebo and basiliximab arms in both studies; although anticipated differences between the two studies (number of African American subjects, number of subjects with Diabetes Mellitus) were seen, the US study demographics were reasonably representative of the [redacted] database statistics for the same period of time. Serologic data for the study populations was well matched between the placebo and basiliximab arms in both studies.

These data are depicted and analyzed on pages 5-12 of this BLA review.

Study Design

Recruitment:

Subjects in study [redacted]

Subjects in study [redacted]

Objectives:

The primary objective of both studies was to determine the effects of [redacted]

Inclusion Criteria.

· Male and non-pregnant female patients, between [redacted]

Exclusion Criteria:

contraception for 12 months (CHIB 201).
· Subjects with positive serology for Hepatitis B (HB-
201).

Follow-up:

Concomitant Therapy

Period	CHIB 352	CHIB 201
Pre- and peri-operative		
Post-operative		
Maintenance		
Rejection		

Disposition of Study Subjects

	CHIB 352		CHIB 201	
	Placebo	Simulect™	Placebo	Simulect™
Randomized				
Randomized and Tx (ITT)				
Mean age (range)				
% Male/Female				
% Race (Cauc/AA/Other)				
Completed 6 months				
Discontinued at 6 months				
Adverse event				
Death				
Withdrawal of consent				
Lost to follow-up				
Other				
Completed 12 months				
Discontinued at 12 months				
Adverse event				
Death				
Withdrawal of consent				
Lost to follow-up				
Other				

21 lines

History of CHIB 201

Variable	Simulect™	Placebo	TOTAL	P-Value #
Cause of ESRD				
Glomerulonephritis				
Pyelonephritis/ Interstitial nephritis				
Polycystic disease				
Hypertension nephrosclerosis				
Diabetes mellitus				
Vasculitis				
Other				
Unknown Origin				
Total Time on Dialysis (months)				
N				
Mean				
S. D				
Current Dialysis				
Hemodialysis				
CAPD				
Both				
Number of Previous Transfusions				
N				
Mean				
S. D				

4 lines

History of ESRD-CHIB 352

Variable	Simulect™	Placebo	TOTAL	P- Value #
Cause of ESRD				
Glomerulonephritis				
Pyelonephritis/ Interstitial nephritis				
Polycystic disease				
Hypertension nephrosclerosis				
Diabetes mellitus				
Vasculitis				
Other				
Unknown Origin				
Total Time on Dialysis (months)				
N				
Mean				
S. D				
Current Dialysis				
Hemodialysis				
CAPD				
Both				
Number of Previous Transfusions				
N				
Mean				
S. D				

13 lines

HLA Matching and Serology-CHIB 201

Variable	Simulect™	Placebo	TOTAL	P-Value #
Total Number of Mismatches				
0				
1				
2				
3				
4				
5				
6				
Panel Reactive Antibodies (%) Most Recent				
N				
Mean				
S. D				
Panel Reactive Antibodies (%) Highest Prev. Level				
N				
Mean				
S. D				

Concomitant Immunosuppressive Medications-CHIB 201

Variable	Simulect™		Placebo	
	Rejection	No Rejection	Rejection	No Rejection
Cyclosporine (ng/ml)				
N				
Mean				
S. D.				
Neoral Dose (mg/kg/day)				
N				
Mean				
S. D.				
Steroid Dose (mg/kg/day)				
N				
Mean				
S. D.				

HLA Matching and Serology-CHIB 352

Variable	Simulect™	Placebo	TOTAL	P-Value #
Total Number of Mismatches				
0				
1				
2				
3				
4				
5				
6				
Panel Reactive Antibodies (%) Most Recent				
N				
Mean				
S. D				
Panel Reactive Antibodies (%) Highest Prev. Level				
N				
Mean				
S. D				

Concomitant Immunosuppressive Medications-CHIB 352

Variable	Simulect™		Placebo	
	Rejection	No Rejection	Rejection	No Rejection
Cyclosporine (ng/ml)				
N				
Mean				
S. D.				
Neoral Dose (mg/kg/day)				
N				
Mean				
S. D.				
Steroid Dose (mg/kg/day)				
N				
Mean				
S. D.				

Cold Ischemia Times-Controlled Clinical Trials

	CHIB 352		CHIB 201	
	Placebo	Simulect™	Placebo	Simulect™
N				
Mean				
S.D.				
P value				

Efficacy was assessed by comparing the percentage of patients in each treatment group that experienced an episode of acute rejection during the first 6 months and 12 months post-transplantation. The percentage of patients experiencing an episode of biopsy-confirmed acute rejection, and the percentage of patients experiencing acute rejection treated with antibody therapy were also compared.

Segment Summary:

According to the phase 3 protocols and the phase 3 summaries in this BLA submission, the primary efficacy endpoint was the Kaplan-Meier (KM) estimate of the percentage of subjects who experienced death, graft loss or an acute rejection episode in the 0-6 months post-transplant. This is in accordance with advisory committee recommendations, using time-to-event analysis. The month 0-6 analysis was based on any events that occurred up to and on Day 180 of the study. An additional analysis was done at 0-12 months, though this was considered secondary. The primary efficacy variable was analyzed using the ITT population. Secondary variables are listed below:

Intent-to-Treat (ITT) Population

- Death
- Death or Graft Loss
- Graft Loss
- First Rejection Episode
- Second Rejection Episode
- First Biopsy Confirmed Rejection Episode
- Death, Graft Loss or First Biopsy Confirmed Rejection Episode
- Graft Loss Preceded by a Rejection Episode
- Graft Loss Preceded by a Rejection Episode Treated with Antibody Therapy
- First Rejection Episode Treated with Antibody Therapy
- First Rejection Episode Treated with Antibody Therapy, _____ or Azathioprine
- Distribution of the Number of Rejection Episode (0, 1, 2, 3, 4, 5, >5 episodes)

All Treated Population

- Death
- Death, Graft Loss or First Rejection Episode

(Any subject who was not transplanted was designated as a graft loss on Day 1 for the analyses. This designation was not done for the intent-to-treat population because the affected subjects did not meet the definition of intent-to-treat which required a subject have a transplant.)

Comment:

SIMULECT™, in combination with Neoral® and steroids, produced statistically significant reductions in the incidence of acute rejection, biopsy-confirmed acute rejection, and acute rejection treated with antibody therapy during the first 6 months and 12 months post-transplantation. Table 1 summarizes the results of these studies. The table shows (1) the percentage of patients experiencing acute rejection, (2) the percentage of patients experiencing biopsy-confirmed acute rejection, and (3) the percentage of patients experiencing acute rejection which was treated with antibody therapy, for each study and for the pooled studies within the first 6 months and 12 months post-transplantation. Figure 1 displays the Kaplan-Meier estimates of the percentage of patients by treatment group experiencing acute rejection during the first 12 months post-transplantation for the pooled studies.

Segment Summary:

CRFs and Line Listings were reviewed for accuracy. This review yielded no specific concerns; none of the subjects required reclassification with respect to outcome. Primary and selected secondary endpoints were reanalyzed by the agency and found to be in agreement with the analysis of the sponsor.

These data, as well as additional exploratory analyses performed by the agency, are depicted on pages 13-17 of this BLA review.

11 lines

Efficacy; months 0-6 post-transplantation: During the first 6 months post- transplantation, in Study 201, the incidence of acute rejection was proportionately reduced by 35% in patients treated with SIMULECT™ (SIMULECT™: 34% vs. placebo: 52%; p< 0.001); the incidence of biopsy- confirmed acute rejection was reduced by 32% (SIMULECT™: 30% vs. placebo 44%, p= 0.007); and the incidence of acute rejection treated with antibody therapy was reduced by 56% (SIMULECT™: 10% vs. placebo: 23%, p= 0.001). In Study 352, the incidence of acute rejection was reduced by 33% in patients treated with SIMULECT™ (SIMULECT™: 35% vs. placebo: 52%, p= 0.002); the incidence of biopsy-confirmed acute rejection was reduced by 28% (SIMULECT™: 33% vs. placebo 46%, p= 0.015); and the incidence of acute rejection treated with antibody therapy was reduced by 36% (SIMULECT™: 18% vs. placebo: 28%, p= 0.041).

Efficacy; months 0-12 post-transplantation: The benefit of treatment with SIMULECT™ was maintained throughout the first 12 months post-transplantation. In Study 201, the incidence of acute rejection was proportionately reduced by 31% (p= 0.001); the incidence of biopsy-confirmed acute rejection was reduced by 30% (p= 0.005); and the incidence of acute rejection treated with antibody therapy was reduced by 52% (p= 0.001). In Study 352, the incidence of acute rejection was reduced by 31% (p= 0.001); the incidence of biopsy-confirmed acute rejection was reduced by 29% (p= 0.009); and the incidence of acute rejection treated with antibody therapy was reduced by 31% (p= 0.034).

Comment: These data are supported by primary data presented in the BLA document.

Overall graft survival at 1 year did not differ between the treatment groups. However the rate of graft loss for immunological reasons (including acute, hyperacute, and chronic rejection) was 3.6% (13/ 363) in the SIMULECT™-treated group and 5.8% (21/ 359) in the placebo-treated group.
The clinical benefit of SIMULECT™ was evident regardless of age, gender, or donor type (cadaveric or living-donor allograft). The clinical benefit of SIMULECT™ was evident in known high-risk groups such as Black patients and patients with diabetes mellitus.

Comment: The statement on overall 1 year graft survival are supported by primary data presented in the BLA document.

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Primary and Secondary Efficacy Endpoints; Intent-to-Treat; Month 0-6; CHIB 201

Endpoint	Simulect™	Placebo	P-Value#
Primary Endpoint			
Death, Graft Loss or First Rejection Episode			
Secondary Endpoints			
Death			
Death or Graft Loss			
Graft Loss			
First Rejection Episode			
Second Rejection Episode			
First Biopsy Confirmed Rejection Episode ##			
Death, Graft Loss or First Biopsy Confirmed Rejection Episode			
Graft Loss Preceded by a Rejection Episode			
Graft Loss Preceded by a Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy, , or Azathioprine			

Primary and Secondary Efficacy Endpoints; Intent-to-Treat; Month 0-6; CHIB 352

Endpoint	Simulect™	Placebo	P-Value#
Primary Endpoint			
Death, Graft Loss or First Rejection Episode			
Secondary Endpoints			
Death			
Death or Graft Loss			
Graft Loss			
First Rejection Episode			
Second Rejection Episode			
First Biopsy Confirmed Rejection Episode			
Death, Graft Loss or First Biopsy Confirmed Rejection Episode			
Graft Loss Preceded by a Rejection Episode			
Graft Loss Preceded by a Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy, r Azathioprine			

Chi- square test.
Number in parenthesis are percentages.

Primary and Secondary Efficacy Endpoints; Intent-to-Treat; Month 0-12; CHIB 201

Endpoint	Simulect™	Placebo	P-Value#
Primary Endpoint			
Death, Graft Loss or First Rejection Episode			
Secondary Endpoints			
Death			
Death or Graft Loss			
Graft Loss			
First Rejection Episode			
Second Rejection Episode			
First Biopsy Confirmed Rejection Episode ##			
Death, Graft Loss or First Biopsy Confirmed Rejection Episode			
Graft Loss Preceded by a Rejection Episode			
Graft Loss Preceded by a Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy, or Azathioprine			

Primary and Secondary Efficacy Endpoints; Intent-to-Treat; Month 0-12; CHIB 352

Endpoint	Simulect™	Placebo	P-Value#
Primary Endpoint			
Death, Graft Loss or First Rejection Episode			
Secondary Endpoints			
Death			
Death or Graft Loss			
Graft Loss			
First Rejection Episode			
Second Rejection Episode			
First Biopsy Confirmed Rejection Episode			
Death, Graft Loss or First Biopsy Confirmed Rejection Episode			
Graft Loss Preceded by a Rejection Episode			
Graft Loss Preceded by a Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy			
First Rejection Episode Treated with Antibody Therapy Azathioprine			

Chi- square test.
Number in parenthesis are percentages.

Distribution of Rejection Episodes; Controlled Clinical Trials; Month 0-6

Number of	CHIB 352		CHIB 201	
Rejection Episodes	Placebo	Simulect™	Placebo	Simulect™
0				
1				
2				
3				
4				
5				
>5				
P value				

Distribution of Rejection Episodes; Controlled Clinical Trials; Month 0-12

Number of	CHIB 352		CHIB 201	
Rejection Episodes	Placebo	Simulect™	Placebo	Simulect™
0				
1				
2				
3				
4				
5				
>5				
P value				

G lines

Total Number of Mismatches	Simulect™	Placebo
0		
1		
2		
3		
4		
5		
6		

Safety Review:

SIMULECT™ does not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and the concurrent administration of

immunosuppressants and other medications. In both controlled, double-blind, multicenter trials, the pattern of adverse events in 363 SIMULECT™-treated patients was indistinguishable from that of 359 placebo-treated patients.

Cytokine release syndrome, anaphylaxis or other infusion-related adverse events have not been observed.

Comment: The second paragraph (sentence) is supported by primary data presented in the BLA document, ---

The incidence of adverse events for SIMULECT™ was determined in two randomized comparative double-blind trials in the prevention of rejection in renal transplantation patients. Both the acute tolerability and the adverse event profiles were comparable in the SIMULECT™ and placebo treatment groups during these two studies. The cumulative incidence of adverse events which occurred in >10% in either treatment group during the first 12 months post-transplantation for the pooled studies is summarized in Table 2. The rates of malignancies, reported infections, serious infections, and infectious organisms were similar in the SIMULECT™ and placebo treatment groups. No specific SIMULECT™-related risk was identified.

Segment Summary:

Adverse events were recorded and coded by the sponsor for each subject using the ---
---). The number and percent of patients with treatment emergent signs and symptoms (adverse events) were summarized by body system and preferred term. The name of the microorganisms recorded on the Infections case report form were coded using the --- dictionary. Pathologic diagnoses were coded from local pathology reports. The agency reviewed CRFs and Line Listings for accuracy; this review yielded no specific concerns.

Adverse events were analyzed by specific diagnosis, category, time of onset, and organ system/etiology. These analyses are depicted on pages 20-30 of this BLA review.

Overall Incidence of Adverse Events; Intent-to-Treat; Month 0-12; CHIB 201

Event	Simulect™	Placebo
Any Adverse Events or Rejection Episodes	188 (99%)	182 (98%)
Any Adverse Events	188 (99%)	182 (98%)
Any Adverse Events Excluding Infections and Thrombotic Events	182 (96%)	177 (95%)
Any Infections	165 (87%)	164 (88%)
Any Thrombotic Events	25 (13%)	23 (12%)
Any Severe Adverse Events	92 (48%)	85 (46%)
Any Drug Related# Adverse Events	76 (40%)	73 (39%)
Any Serious Adverse Events	120 (63%)	119 (64%)

Identified by the investigator as possibly, probably, or definitely related to study medication.

Overall Incidence of Adverse Events; Intent-to-Treat; Month 0-12; CHIB 352

Event	Simulect™	Placebo
Any Adverse Events or Rejection Episodes	173 (100%)	173 (100%)
Any Adverse Events	173 (100%)	173 (100%)
Any Adverse Events Excluding Infections and Thrombotic Events	173 (100%)	173 (100%)
Any Infections	129 (75%)	127 (73%)
Any Thrombotic Events	11 (6%)	21 (12%)
Any Severe Adverse Events	73 (42%)	71 (41%)
Any Drug Related# Adverse Events	47 (27%)	61 (35%)
Any Serious Adverse Events	94 (54%)	106 (61%)

Identified by the investigator as possibly, probably, or definitely related to study medication.

Comment: Overall incidence data from the two studies were well balanced between treatment and placebo groups. Subgroup analysis by age, gender (both studies), race, and type of donor (analysis restricted to ———) showed no significant, consistent, treatment-related effects.

Comment: Treatment emergent adverse events included any adverse event that started on or after day 0 but was not present before day 0 or that started before day 0 and increased in severity on or after day 0. **This definition captures all adverse events potentially related to treatment, and is the primary capture definition for the safety analysis of Simulect™.** Common treatment emergent adverse events were defined as those adverse events that occurred in >10% of patients in the Simulect™ treatment group during months 0 to 12 of the study; these are shown in tabular form for the two controlled studies on the next three pages. No significant, consistent, treatment-related effects were seen.

Comment: Subgroup analysis of common treatment emergent adverse events by age, gender (both studies), race and type of donor (analysis restricted to ——— showed no significant, consistent, treatment-related effects.

Number and Percent of Subjects with Common Treatment Emergent Adverse Events
Intent-to-Treat; Month 0-12; CHIB 201

Body System/ Preferred Term	Simulect™	Placebo	Difference	Difference##
BODY AS A WHOLE-GENERAL DISORDERS				
FEVER				
INFECTION VIRAL				
EDEMA				
EDEMA LEGS				
PAIN				
CARDIOVASCULAR DISORDERS, GENERAL				
HYPERTENSION				
CENTRAL AND PERIPHERAL NERVOUS SYST. DIS				
HEADACHE				
GASTRO-INTESTINAL SYSTEM DISORDERS				
ABDOMINAL PAIN				
CONSTIPATION				
DIARRHEA				
NAUSEA				
VOMITING				
METABOLIC AND NUTRITIONAL DISORDERS				
HYPERKALEMIA				
HYPERURICEMIA				
HYPOKALEMIA				
PSYCHIATRIC DISORDERS				
INSOMNIA				
RED BLOOD CELL DISORDERS				
ANEMIA				
RESPIRATORY SYSTEM DISORDERS				
DYSPNEA				
UPPER RESP TRACT INFECTION				
SKIN AND APPENDAGES DISORDERS				
HERPES SIMPLEX				
SURGICAL WOUND COMPLICATION				
URINARY SYSTEM DISORDERS				
SURGERY				
URINARY TRACT INFECTION				

Number and Percent of Subjects with Common Treatment Emergent Adverse Events
Intent-to-Treat; Month 0-12; CHIB 352

Body System/ Preferred Term	Simulect™	Placebo	Difference	Difference##
BODY AS A WHOLE-GENERAL DISORDERS				
ASTHENIA				
CHEST PAIN				
DRUG LEVEL INCREASED				
FATIGUE				
FEVER				
EDEMA				
EDEMA GENERALISED				
EDEMA PERIPHERAL				
PAIN				
CARDIOVASCULAR DISORDERS, GENERAL				
HYPERTENSION				
HYPOTENSION				
CENTRAL AND PERIPHERAL NERVOUS SYST. DIS				
DIZZINESS				
HEADACHE				
PARESTHESIA				
TREMOR				
GASTRO-INTESTINAL SYSTEM DISORDERS				
ABDOMEN ENLARGED				
ABDOMINAL PAIN				
CONSTIPATION				
DIARRHEA				
DYSPEPSIA				
MONILIASIS				
NAUSEA				
VOMITING				
HEART RATE AND RHYTHM DISORDERS				
TACHYCARDIA				
METABOLIC AND NUTRITIONAL DISORDERS				
ACIDOSIS				
DEHYDRATION				
HYPERCHOLESTEROLEMIA				
HYPERGLYCEMIA				
HYPERKALEMIA				
HYPERLIPEMIA				
HYPOCALCEMIA				
HYPOKALAEMIA				
HYPOMAGNESAEMIA				
HYPOPHOSPHATAEMIA				
WEIGHT INCREASE				
MUSCULO-SKELETAL SYSTEM DISORDERS				
ARTHRALGIA				
BACK PAIN				
CRAMPS				
PAIN LEG(S)				

PSYCHIATRIC DISORDERS
INSOMNIA
RED BLOOD CELL DISORDERS
ANEMIA
POLYCYTHAEMIA
RESPIRATORY SYSTEM DISORDERS
CHEST SOUNDS ABNORMAL
COUGHING
DYSPNEA
PHARYNGITIS
RHINITIS
SINUSITIS
UPPER RESP TRACT INFECTION
SKIN AND APPENDAGES DISORDERS
ACNE
PRURITUS
RASH
SKIN DISORDER
SURGICAL WOUND COMPLICATION
URINARY SYSTEM DISORDERS
BLADDER DISORDERS NOS
DYSURIA
HEMATURIA
NPN INCREASED
OLIGURIA
URINARY TRACT INFECTION

The incidence of malignancies among the 722 ITT patients in the two 12- month controlled trials was not significantly different between the SIMULECT™ and placebo-treatment groups, and compared to the incidence reported in the literature for renal allograft recipients. Overall, lymphoma/lymphoproliferative disease occurred in 1 patient (0.3%) in the SIMULECT™ group compared with 2 patients (0.6%) in the placebo group. Other malignancies were reported among 5 patients (1.4%) in the SIMULECT™ group compared with 7 patients (1.9%) in patients treated with placebo.

Comment: Specific adverse events categories of interest include infections, malignancies, death, and immunogenicity. These are treated separately below:

Infections

Data are shown for i) the number and percent of subjects with infections by body system, with selected subheadings, ii) distribution of the number of infections by subject, and iii) distribution of the number of infections by organism. These data are provided in tabular form for the ITT populations for CHIB 201 and CHIB 352 (the next 4 pages).

4 pgs

Number and Percent of Subjects with Infections by Body System-With Selected Subheadings Shown
Intent-to-Treat; Month 0-12; CHIB 201

Body System/ Preferred Term	Simulect™	Placebo	Difference	of the Difference#
At least one Infection				
BODY AS A WHOLE - GENERAL DISORDERS				
FEVER				
INFECTION				
INFECTION BACTERIAL				
INFECTION FUNGAL				
INFECTION PARASITIC				
INFECTION VIRAL				
MONILIASIS				
SEPSIS				
CENTRAL AND PERIPHERAL NERVOUS SYST. DIS				
ENDOCRINE DISORDERS				
SIALOADENITIS				
GASTRO-INTESTINAL SYSTEM DISORDERS				
MONILIASIS				
MONILIASIS GI				
HEARING AND VESTIBULAR DISORDERS				
LIVER AND BILIARY SYSTEM DISORDERS				
MUSCULO-SKELETAL SYSTEM DISORDERS				
REPRODUCTIVE DISORDERS, FEMALE				
MONILIASIS GENITAL				
REPRODUCTIVE DISORDERS, MALE				
RESPIRATORY SYSTEM DISORDERS				
BRONCHITIS				
PNEUMONIA				
SINUSITIS				
UPPER RESP TRACT INFECTION				
SKIN AND APPENDAGES DISORDERS				
HERPES SIMPLEX				
HERPES ZOSTER				
SURGICAL WOUND COMPLICATION				
URINARY SYSTEM DISORDERS				
PYELONEPHRITIS				
URINARY TRACT INFECTION				
VASCULAR (EXTRACARDIAC) DISORDERS				
VISION DISORDERS				
CONJUNCTIVITIS				

Distribution of the Number of Infections; Intent-to-Treat; Month 0-12; CHIB 201

Number of Infections Per Subject	Simulect™	Placebo	P-value#
0			
1			
2			
3			
4			
>4			

Center adjusted test on rank scores.

Distribution of the Number of Infections by Category of Organism; Intent-to-Treat; Month 0-12;

	Simulect™	Placebo	P-value#
All Infections			
1			
2			
3			
4			
>4			
All Bacterial Infections			
1			
2			
3			
4			
>4			
All Viral Infections			
1			
2			
3			
4			
>4			
All Fungal Infections			
1			
2			
3			
4			
>4			
All Other Infections			
1			
2			
3			
4			
>4			
All Missing Infections			
1			
2			
3			
4			
>4			

Center adjusted test on rank scores.

Number and Percent of Subjects with Infections by Body System-Subset Selected
Intent-to-Treat; Month 0-12; CHIB 352

Body System/ Preferred Term	Simulect™	Placebo	Difference	of the Difference#
At least one Infection				
BODY AS A WHOLE-GENERAL DISORDERS				
INFECTION				
INFECTION BACTERIAL				
INFECTION FUNGAL				
INFECTION PARASITIC				
INFECTION VIRAL				
SEPSIS				
CENTRAL AND PERIPHERAL NERVOUS SYST. DIS				
GASTRO-INTESTINAL SYSTEM DISORDERS				
ABSCESS				
GASTRO-INTESTINAL DISORDER NOS				
GASTROENTERITIS				
MONILIASIS				
MONILIASIS GI				
ESOPHAGITIS				
PERITONITIS				
HEARING AND VESTIBULAR DISORDERS				
OTITIS MEDIA				
MUSCULO-SKELETAL SYSTEM DISORDERS				
OSTEOMYELITIS				
MYO-,ENDO-,PERICARDIAL AND VALVE DISOR				
REPRODUCTIVE DISORDERS, FEMALE				
MONILIASIS GENITAL				
VAGINITIS				
REPRODUCTIVE DISORDERS, MALE				
RESPIRATORY SYSTEM DISORDERS				
BRONCHITIS				
PNEUMONIA				
RHINITIS				
SINUSITIS				
UPPER RESP TRACT INFECTION				
SKIN AND APPENDAGES DISORDERS				
CELLULITIS				
DERMATITIS FUNGAL				
HERPES SIMPLEX				
HERPES ZOSTER				
SKIN DISORDER				
SURGICAL WOUND COMPLICATION				
URINARY SYSTEM DISORDERS				
PYELONEPHRITIS				
URINARY TRACT INFECTION				
VASCULAR (EXTRACARDIAC) DISORDERS				
VISION DISORDERS				
CONJUNCTIVITIS				
RETINITIS				

Distribution of the Number of Infections: Intent-to-Treat; Month 0-12; CHIB 352

Number of Infections Per Subject	Simulect™	Placebo	P-value#
0			
1			
2			
3			
4			
>4			

Center adjusted — test on rank scores.

Distribution of the Number of Infections by Category of Organism; Intent-to-Treat; Month 0-12;

	Simulect™	Placebo	P-value#
All Infections			
1			
2			
3			
4			
>4			
All Bacterial Infections			
1			
2			
3			
4			
>4			
All Viral Infections			
1			
2			
3			
4			
>4			
All Fungal Infections			
1			
2			
3			
4			
>4			
All Other Infections			
1			
2			
3			
4			
>4			
All Missing Infections			
1			
2			
3			
4			
>4			

Center adjusted — test on rank scores.

11 lines

Serious CMV Infections by Donor and Recipient CMV Status at Baseline; Intent-to-Treat; Month: 0- 12

Donor/ Recipient CMV Status at Baseline	Simulect™	Placebo	Difference	of the Difference
Donor+ & Recipient-				
Donor+ & Recipient+				
Donor- & Recipient+				
Donor- & Recipient-				
All				

Malignancies

Four malignancies occurred in the Simulect group at month 12; a corresponding 3 malignancies occurred in the placebo group.

Subject	Treatment	Neoplasm (onset day)

Two malignancies occurred in the Simulect group at month 12; a corresponding 6 malignancies occurred in the placebo group.

Subject	Treatment	Neoplasm (onset day)

Comment: The overall incidence and types of malignancies appear comparable between the treatment groups.

Comment: There was no apparent increase in the incidence of PTLD related to treatment with Simulect.

Death

Nine deaths occurred in the Simulect group at month 12; a corresponding 5 deaths occurred in the placebo group.

Subject	Treatment	Cause of death (day)

Five deaths occurred in the Simulect group at month 12; a corresponding 7 deaths occurred in the placebo group.

Subject	Treatment	Cause of death (day)

Comment: The overall incidence and causes of deaths appear comparable between the treatment groups.

Immunogenicity

Analyses conducted for this BLA submission are summarized below.

Study	Transplant type	Number Screened	HACA	Human Ig	Xenogeneic Ig	HAMA
[redacted]	Renal	24	0	1	2	--
[redacted]	Renal	37	1	0	4	--
[redacted]	Renal	30	0	--	--	--
[redacted]	Renal	172	0	--	--	6
[redacted]	Liver	24	0	--	--	--
Totals			1/ 270	1/ 61	6/ 61	6/ 172

HACA=human anti-chimeric antibody (anti-idiotype); HAMA=human anti-mouse antibody; --screening not performed.

Comment: Overall immunogenicity was very low. While the incidence of HAMA and HACA was too low to evaluate potential negative pharmacodynamic effects, no obvious trends were seen.

The following adverse events, not mentioned in the table above, were reported with an incidence of ≥3% in patients treated with SIMULECT™ in the two controlled clinical trials; the frequency of these was similar in the SIMULECT™ and placebo treatment groups: Body as a Whole: accidental trauma, chest pain, drug level increased, face edema, fatigue, infection, malaise, edema generalized, rigors, sepsis; Cardiovascular: angina pectoris, cardiac failure, chest pain, heart sounds abnormal, hypertension aggravated; Nervous System: hypoesthesia, neuropathy, paraesthesia; Endocrine: glucocorticoids increased; Gastro-Intestinal: abdomen enlarged, flatulence, gastro-intestinal disorder, gastroenteritis, GI hemorrhage, gum hyperplasia, melena, esophagitis, stomatitis ulcerative; Heart Rate and Rhythm: arrhythmia, fibrillation atrial, tachycardia; Metabolic and Nutritional: dehydration, diabetes mellitus, fluid overload, hypercalcemia, hyperlipemia, hypoglycemia, hypoproteinemia; Musculo-Skeletal: arthralgia, arthropathy, bone fracture, cramps, hernia, myalgia; Platelet and Bleeding: hematoma, hemorrhage, purpura, thrombocytopenia, thrombosis; Psychiatric: agitation, anxiety, depression; Red Blood Cell: polycythemia; Reproductive Disorders, Male: impotence, edema genital; Respiratory: bronchitis, bronchospasm, chest sounds abnormal, pneumonia, pulmonary disorder, pulmonary edema, sinusitis; Skin and Appendages: cyst, herpes simplex, herpes zoster, hypertrichosis, pruritus, rash, skin disorder, skin ulceration; Urinary: albuminuria, micturition frequency, oliguria, renal function abnormal, renal tubular necrosis, ureteral disorder, urinary retention; Vascular Disorders: vascular disorder; Vision Disorders: cataract, conjunctivitis, vision abnormal.

Comment: This paragraph is supported by primary data presented in the BLA document.

***OVERDOSAGE** In clinical studies SIMULECT™ has been administered to transplantation patients in single doses of up to 60 mg and cumulative multiple doses of up to 150 mg over 24 days with no untoward acute effects.*

Comment: This paragraph is supported by primary data presented in the BLA document.

PRECAUTIONS

Drug Interactions

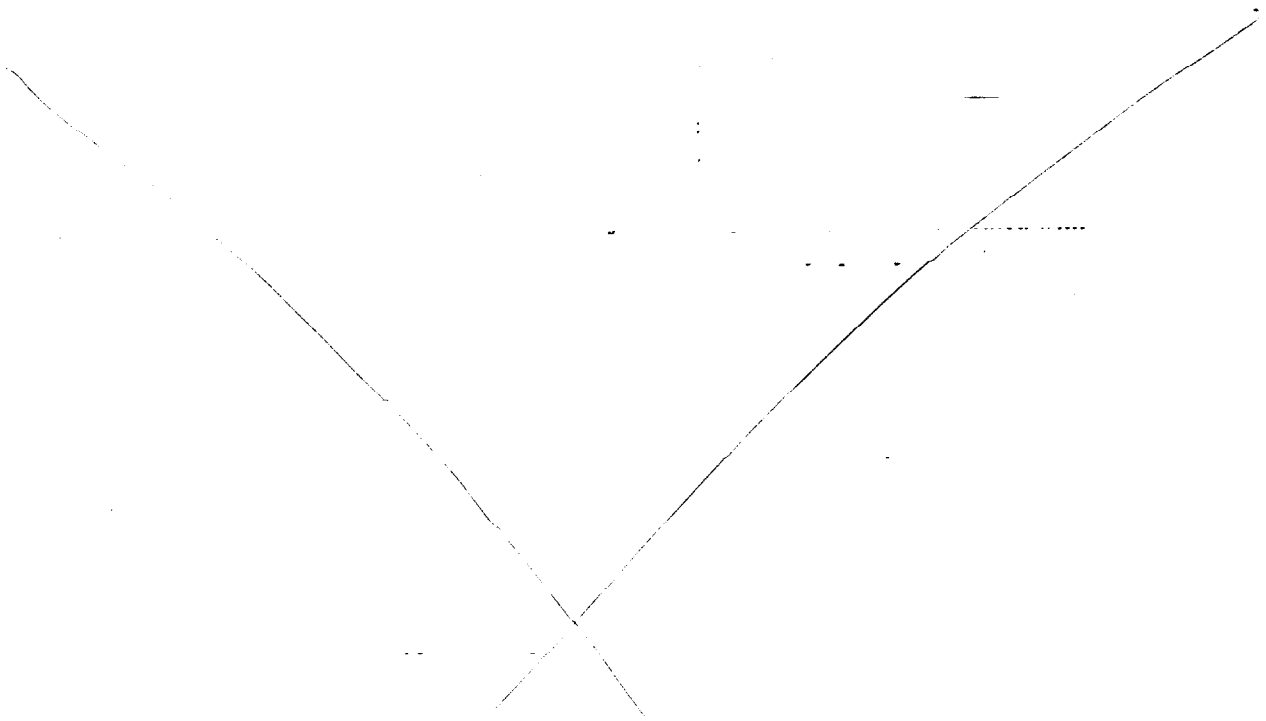
Because SIMULECT™ is an immunoglobulin, no metabolic interactions are to be expected. Therefore, no formal drug-drug interaction studies have been conducted.

In controlled clinical trials a limited number of patients, treated with the recommended dose of SIMULECT™, have also been administered azathioprine, mycophenolate mofetil, [redacted] or antibody therapy such as OKT3 or ATG/ALG.

Comment: This paragraph is supported by primary data presented in the BLA document

Azathioprine and Mycophenolate Mofetil: During the first 6 months post- transplantation, 24.5% of patients in the SIMULECT™ group and 34.3% of patients in the placebo group were treated with azathioprine or mycophenolate mofetil. No patients in the SIMULECT™ group who received azathioprine or mycophenolate experienced lymphoma or any other malignancy during the first 12 months post-transplantation.

Comment: This paragraph is supported by primary data presented in the BLA document.



DOSAGE AND ADMINISTRATION
SIMULECT™ is for intravenous administration only. Reconstituted SIMULECT™ can be administered as an intravenous infusion over 20 to 30 minutes or as a bolus injection.

Comment: This paragraph is supported by primary data presented in the BLA document.

De Novo Renal Transplantation (Adult)
In adult patients, the recommended total dose is 40 mg, given in two doses of 20 mg each. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The second 20 mg dose should be given 4 days after transplantation.

Comment: This paragraph is supported by primary data presented in the BLA document.

of 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The second dose should be given 4 days after transplantation.

Comment: Please see review of sections 6-"human pharmacokinetics and bioavailability."

Related Label Sections:

INDICATIONS AND USAGE
De Novo Renal Transplantation
SIMULECT™ is indicated for the prophylaxis of organ rejection in de novo renal transplantation. SIMULECT™ should be used with Neoral® (cyclosporine for microemulsion) and corticosteroid-based immunosuppression.

Comment: This paragraph is supported by primary data presented in the BLA document.

CONTRAINDICATIONS
SIMULECT™ is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation. See composition of SIMULECT™ under DESCRIPTION.
WARNINGS
General SIMULECT™ should be prescribed only by physicians who are experienced in the use of immunosuppressive therapy following organ transplantation.
Although no anaphylactic reaction occurred in patients receiving SIMULECT™ in clinical trials, SIMULECT™ is a potential antigenic agent, and physicians must be well-equipped to assess and manage the patient should any anaphylactic reactions occur.

Comment: In keeping with precedent for immunosuppressive agents, the labeling document should include a box warning; this box warning should use wording similar (if not identical) to that used in the labeling of Zenapax (daclizumab). The remainder of the statements are supported by primary data presented in the BLA document.

SIMULECT™ (basiliximab) Powder for Injection is a chimeric (murine/human) monoclonal antibody ($IgG_{1\kappa}$), produced by recombinant DNA technology, that specifically binds to and blocks the interleukin-2 receptor α-chain (IL-2Rα, also known as CD25 antigen) on the surface of T-lymphocytes. It is a sterile, purified glycosylated protein. Based on the amino acid sequence, the molecular weight of the protein is 144,345 Daltons, without post-translational modification. It is obtained from fermentation of an established mouse myeloma cell line genetically engineered to bear plasmids containing the human constant region genes of heavy and light chain, and mouse variable genes specific for IL-2Rα.

The active ingredient, basiliximab, is water soluble. The drug product, SIMULECT™, Powder for Injection, is a lyophilisate which is available in 6 mL colorless glass vials containing an equivalent of 20 mg of active ingredient. Each vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate, 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP.

The 20 mg vial is for use by intravenous bolus injection or infusion.

SIMULECT™ functions as a selective immunosuppressive agent.

To prepare the infusion/injection solution, add 5 mL of Sterile Water for Injection, USP, to the vial containing the SIMULECT™ powder. Shake the vial gently to dissolve the powder. It is recommended that the solution be used as soon as possible after reconstitution, but it may be stored for 24 hours at controlled room temperature, 59° to 86° F (15° to 30°C). Discard the reconstituted solution if not used within 24 hours.

The reconstituted solution is isotonic and may be given as a bolus injection or diluted to a volume of 50 mL or greater with normal saline or dextrose 5% for infusion.

Since no data are available on the compatibility of SIMULECT™ with other intravenous substances, SIMULECT™ should not be mixed with other medications/substances and should always be given through a separate infusion line.

Compatibility with the following infusion sets has been verified:
Infusion Bag:
Baxter minibag NaCl 0.9%
Infusion Sets:
Luer Lock™, H. Noolens
Sterile vented i.v. set, Abbott
infusion set, Codan
Infusomat™, Braun
Infusionsgerat R 87 plus, Ohmeda
Lifecare 5000™ Plumset Microdrip, Abbott
Vented basic set, Baxter
Flashball device, Baxter
Vented primary administration set, Imed
Compatibility with other commercial devices has not been tested.

SIMULECT™ Powder for Injection SIMULECT™ (basiliximab), 20 mg per vial. Each box contains 1 SIMULECT™ single dose vial (NDC No. 0078 0331 84). Store lyophilized SIMULECT™ under refrigerated conditions (2 to 8°C; 36 to 46° F Do not use beyond the expiraion (sic) *date stamped on the vial.*

Comment: Please see review of section 3-"chemistry, manufacturing, and controls."

SIMULECT™ is a chimeric (murine/human) monoclonal antibody selectively targeted against IL-2Rα, which is expressed on the surface of activated T-lymphocytes in response to antigenic challenge. This specific binding of SIMULECT™ to IL-2Rα competitively inhibits the subsequent binding of interleukin-2, which signals T-cell proliferation.

Antibody Responses Of 270 (246 renal; 24 liver) patients treated with SIMULECT™ and tested for anti-idiotype antibodies, only one developed an anti-idiotype antibody response. Of 172 renal transplantation patients treated with SIMULECT™ in one clinical study, the incidence of human anti-murine antibody (HAMA) was 3.5% (6/172); since 4 of the 6 patients positive for HAMA also received OKT3, the incidence may be as low as 1.2% (2/172).

Complete and consistent blocking of IL-2Rα is maintained as long as serum SIMULECT™ levels exceed 0.2 μg/mL (by ELISA). As concentrations fall below this level, expression of IL-2Rα returns to pretherapy values within 1-2 weeks. In vitro studies using human tissues indicate that SIMULECT™ binds only to lymphocytes and macrophages/monocytes.

Single-dose and multiple-dose pharmacokinetic studies have been conducted in patients undergoing kidney transplantation. Cumulative doses ranged from 15 mg up to 150 mg.

Peak serum concentration following intravenous infusion of 20 mg over 30 minutes is 7.1 ± 5.1 mg/L. There is a dose-proportional increase in C_{max} and AUC up to the highest tested single dose of 60 mg.

The volume of distribution at steady state is 8.6 ± 4.1 L. The extent and degree of distribution to various body compartments have not been fully studied.

The terminal half-life is 7.2 ± 3.2 days. Total body clearance is 41 ± 19 mL/h.

No clinically relevant influence of body weight or gender on distribution volume or clearance has been observed in adult patients. Elimination half-life was not influenced by age (20-69 years), gender or race. The median duration of IL-2Rα suppression was 35 days (range 23-45 days).

In one clinical study in 8 pediatric de novo renal transplantation patients 2-12 years of age (up to 37 kg) the central distribution volume was 1.7 ± 0.6 L, half-life was 9.4 ± 4.9 days and clearance was 20 ± 4 mL/h. Clearance and volume were not influenced by age (2-12 years), body weight (9-37 kg) or body surface area (0.44-1.20 m^2). The disposition of Simulect™ in pediatric renal transplantation patients was characterized by an average 50% lower clearance compared to adult patients, whereas the relationship between serum concentration and receptor saturation was similar in both age groups.

A multiple-dose pharmacokinetic study has been conducted in 23 patients undergoing liver transplantation. SIMULECT™ was administered as either a bolus injection or infusion with the first dose administered within 6 hours after reperfusion of the graft. The total dose administered was 40 mg (4 x 10 mg or 2 x 20 mg). No difference in exposure (AUC) was observed between the two dosage regimens. Disposition in adult liver transplantation patients is characterized by a steady-state distribution volume of 7.5 ± 2.5 L, half-life of 4.1 ± 2.1 days, and clearance of 75 ± 24 mL/h. Contributing to clearance were drug loss via drained ascites fluid and post-operative bleeding. Offsetting the faster drug clearance was a lower receptor-saturating concentration threshold of 0.1 μg/mL in this population. Hence, the duration of IL-2Rα blockade at a given SIMULECT™ dose level is similar to that seen in adult renal transplantation patients.

No mutagenic potential of SIMULECT™ was observed in the in vitro assays with Salmonella (Ames) and V79 Chinese hamster cells. No long-term or fertility studies in laboratory animals have been performed to evaluate the potential of SIMULECT™ to produce carcinogenicity or fertility impairment, respectively.

There are no adequate and well-controlled studies in pregnant women. However, no maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgous monkeys 100 days post coitum following intravenous bolus injections of up to 5 mg/kg basiliximab administered twice weekly during the organogenesis period. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No studies have been performed in pregnant or lactating women. Because SIMULECT™ is an immunoglobulin G ($IgG_{1κ}$) antibody, it may cross the human placenta and may be excreted in human milk. Women receiving SIMULECT™ should not breast feed for 8 weeks following the second dose.

The safety and effectiveness of SIMULECT™ have been established in pediatric renal transplantation patients aged 2 to 12 years of age. Use of SIMULECT™ in these age groups is supported by evidence from adequate and well-controlled studies of SIMULECT™ in adults with additional clinical pharmacology data in patients 2 to 12 years of age. The available pharmacokinetic data in children aged 2 years and over is described in the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections. No studies have been performed in neonates or infants aged less than 2 years.

No toxicity was observed when rhesus monkeys received intravenous doses of baxiliximab up to 5 mg/kg twice weekly for 4 weeks. Maximum serum concentrations (C_{max}) in the monkey were approximately 17 times higher after a single dose and 38 times higher after 4 weeks of dosing, compared to C_{max} values in adult renal transplantation patients receiving the recommended clinical dose of SIMULECT™ with concomitant immunosuppressive therapy.

Comment: Please see review of sections 5 & 6-"nonclinical pharmacology, toxicology, and drug metabolism and pharmacokinetic data" & "human pharmacokinetics and bioavailability."

Summary & Conclusions:

This document has reviewed and summarized the clinical efficacy and safety data of the BLA application of Simulect® (basiliximab, 97-1251) for use in the prevention of acute rejection episodes in *de novo* renal transplant patients receiving concomitant immunosuppression with steroids and Neoral® (cyclosporine for microemulsion). All statements in the labeling document concerning the clinical safety and efficacy data are supported by the primary data presented in the BLA document. Additional analyses performed within the agency confirm and support the safety and efficacy data presented by the sponsor in this BLA submission.

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DETERMINED
TO BE NOT
RELEASABLE

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